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LOWRIE, LANDO & ANASTASI, LLP
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@ll-a.com
gengelson@ll-a.com

Office Action Summary	Application No.	Applicant(s)	
	10/656,350	LADNER ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-18 and 20-28 are pending in the instant application and are the subject of the Office Action below.

Objection to Applicants' Claim Identifiers Under 37 C.F.R. § 1.121

The objection to the status identifiers in Applicants' claims is withdrawn in view of the proper status identifier "canceled" for claims 29-38.

Claim Rejections - 35 USC § 102 – Withdrawn in view of Applicants' Amendment

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

<u>*The rejection of the claims as anticipated by Ladner is withdrawn*</u>:

The rejection of claims 1-4, 8, 9, 13, 15-17 and 20-27 under 35 U.S.C. § 102(b) as being anticipated by Ladner *et al.*, U.S. Patent No. 5,403,484 A, issued on April 4, 1995, <u>is withdrawn in view of Applicants amendment to the claims</u>.

Applicants have amended the claims to be directed to the particular target *of step (a)*, such as a process that uses the same population of beads having an immobilized target in a reusable target-bead format.

The Examiner agrees that Ladner does not explicitly teach the reusable bead approach, such as that Exemplified in Applicants' Example 2 (Reply, page 8, first two paragraphs). Ladner does teach affinity selection of phage using HNE immobilized to agarose beads (col. 144, lines 18-22), and a subsequent selection using HNE immobilized to agarose beads (col. 144, lines 15-36), however, it is not conclusively clear for the disclosure of Ladner that the second affinity

selection on agarose-immobilized HNE target are the same agarose-immobilized HNE as the first affinity selection. Accordingly, the rejection is withdrawn.

Claim Rejections - 35 USC § 103 – Maintained

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

<u>Claims 1-9, 13, 15-17, 20-27, are obvious over Ladner and Anderson</u>:

The rejection of claims 1-9, 13, 15-17 and 20-27, under 35 U.S.C. § 103(a) as being unpatentable over Ladner *et al.*, U.S. Patent No. 5,403,484 A, issued on April 4, 1995, in view of Anderson, U.S. Patent No. 6,649,419 B1, issued on November 18, 2003, <u>is maintained</u>. The only difference in the instant rejection and the previous rejection of the claims over Ladner and Anderson is the specific addressing of Applicants amendment to claim 1 requiring the "target of step (a)."

Applicants contend that Lander does not teach or suggest producing replicate phage from the infected cells in the presence of target immobilized to the support to produce phage or separating phage that do not bind to the target. Applicants are further of the opinion that combination of Ladner and Anderson also does not teach the claimed invention, including the newly added limitation of binding to the target of step (a), and suggest that the Examiner has

provided no rationale as to why one of ordinary skill in the art would combine the teachings of Ladner and Anderson to arrive at the claimed invention.

The Examiner respectfully disagrees as the Applicants remarks are misplaced. Ladner is directed to the use of phage display in a combinatorial approach for the accelerated discovery of select ligands from a large library of peptides having the highest affinity for human neutrophil elastase (HNE). This process, the process of step-wise enriching ligands from a library against its binding partner, is generally referred to as "biopanning" and is a well-established procedure in the combinatorial arts.

The particular disclosure of Ladner wherein the library of ligands produced by phage display are bound to HNE immobilized to agarose beads for selection and the removal of those phage that do not bind by washing (col. 144, lines 15-36) was detailed in the last Office Action. Following selection of the particular phage to the beads having immobilized target (*i.e.*, HNE), XL1-Blue cells are infected with bound phage, the infected cell result in additional copies of the phage, and the phage produced from the infected cells are subsequently bound to new target immobilized to agarose beads, followed by washing and repeating the process until through phage selection the optimized ligand is identified.

Similar to Ladner, Anderson is directed towards an improved method and composition for binding ligands. In particular, Anderson teaches the advantages of using paramagnetic beads as the solid support for hosting the target:

> "A method and apparatus for extracting, identifying, and manipulating proteins or peptides from a solution uses paramagnetic beads having a coating with an affinity for the target component. In one embodiment, paramagnetic beads coated with C18 are used to adsorb proteins and peptides. ***The beads can be used to purify, immobilize and assay antibodies. By cycling the beads, many times greater molar amount of binding partner may be separated from a solution***. A magnetic probe is used to capture the beads and transfer the beads to selected processing stages."

Anderson, Abstract of the Invention (emphasis added).

Clearly, the disclosures of Ladner and Anderson are analogous as both teachings are directed towards biopanning. While Ladner's claimed invention is directed towards certain phage compositions that are useful in biopanning, Anderson's invention is directed towards an

improved paramagnetic bead hosting a target for the binding and screening of potential binding partners. As explained in the last Office Action, one of ordinary skill in the art would clearly recognize the advantages of Anderson paramagnetic bead for the reasons of reusing the same beads to successively enrich for the desired ligand, such as the ligands used in the biopanning method of Ladner. For the reasons explained by Anderson, the paramagnetic beads would be seen as an improvement over the agarose beads of Ladner, and are taught to be reusable, easily manipulated under a magnetic field, and carried out in the same reaction vessel. These reasons were clearly laid out in the rejection of the previous Office Action, the rejection was proper at the time it was made, and is proper for maintaining the rejection.

Regarding Applicants assertions that claim 20 is not anticipated by Ladner because Ladner teaches a burst size of 100-1000 progeny (Reply, beginning on page 8), the Examiner disagrees.

The claim limitation of "fewer than 5000 progeny phage are produced for each phage member selected in step (b)" is in fact met by Ladner. The "burst size" of 100 to 1000 progeny phage taught in Ladner is clearly less than the claimed "5000 progeny phage" *per phage*. It does not matter how long the incubation period is carried out because the burst size is related to a "per phage" basis as claimed, *i.e.*, a normalized accounting for each plaque formation. The teaching of Ladner referenced by Applicants (*i.e.*, Ladner, col. 118, lines 5-33) is not relevant to this portion of the claim as this teaching is directed to the creation of the initial phage library prior to biopanning, not the biopanning itself. Accordingly, the rejection of claim 20 is proper, as is the rejection of newly amended claim 24 which now also claims "fewer than 5000 progeny phage".

Regarding Applicants assertions that the rationale for rejecting claims 2-4, 8, 9, 13, 15-17 and 20-27 as being obvious were not presented – such assertions are incorrect. On page 8 of the previous Office Action the Examiner clearly indicated that the limitations of claims 1-4, 8, 9, 13, 15-17 and 20-27, and the corresponding teachings of Ladner were incorporated from the 102(b) rejection (previous Office Action, page 8, lines 1-2). The Examiner also carefully laid out the teachings of Anderson showing how closely related the teachings are to Ladner, and how Anderson carefully illustrates the advantages of using target bound to the paramagnetic beads. The Examiner also detailed how one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed and what would be recognized

from the combined teaching of Ladner in view of Anderson (previous Office Action, page 8, line 9 through page 9, line 6).

Accordingly, the rejection is proper and is maintained.

Reiterated Rejection:

The claimed invention is generally directed towards affinity filter screening of phage from a library using a target immobilized to solid substrate. The phage from the library that have affinity towards the immobilized target bind to the solid substrate through the target, while the unbound phage are removed/washed away. The target-bound phage are then used in the bound form to infect host cells, replicated, and screening is repeated using the same target-immobilized substrate, as amended.

More specifically, claim 1 is directed to a method of selecting phage that encode a target binding protein from a plurality of display phage, the method comprising:

a) forming a mixture comprising a plurality of diverse display phage, a target, and a support, wherein each phage of the plurality displays a heterologous protein component on its surface and each phage includes a nucleic acid encoding the heterologous protein component, the heterologous protein component being a member of a set of diverse protein components;

b) forming phage immobilized to the support, each of which comprises a phage from the plurality which binds the target and the target immobilized to the support;

c) separating phage that do not bind to the target from the phage immobilized to the support via binding to the target;

d) contacting host cells with the phage immobilized to the support so that the host cells are infected by the phage immobilized to the support to yield a first population of infected cells;

e) producing replicate phage from the infected cells in the presence of the target immobilized to the support, thereby forming replicate phage immobilized to the support via binding to the target of step (a);

f) separating replicate phage that do not bind to the target of step (a) from the replicate phage immobilized to the support; and

g) contacting host cells with the replicate phage immobilized to the support so that host cells are infected with the replicate phage immobilized to the support to yield a second population of infected cells.

As in part (a) of claim 1, Ladner teaches a method for screening a library of diverse phage (*i.e.*, KLMUT – a diverse library of over 1 x 10^5 phage – col. 143, lines 57-60), each phage displaying heterologous protease inhibitors which are considered diverse protein components, such as EpiNE1 through EpiNE8 (col. 142, line 14 through col. 143, line 56) having binding affinity for a target (*i.e.*, human neutrophil elastase) immobilized to a solid substrate (*i.e.*, agarose beads) – see col. 144, lines 15-36. As in part (b) of claim 1, this section of Ladner teaches that the phage bind to the support through the target; as in part (c), phage that do not bind the target are eluted away (*i.e.*, separated); as in part (d), the particle-bound phage are infected into XL1-Blue™ cells (col. 144, lines 28-30); as in step (e), the previous infection reaction produced 348 plaques which were pooled for further affinity selection with the immobilized HNE-beads, and as in step (f) the non-binding phage are separated from the phage bound to the HNE-beads, and as in step (g), the host cells are contacted with these beads and infected with the phage to form a second population of cells.

As in claims 2 and 3, Ladner teaches recovering the second population of infected cells and recovering the phage from those cells (col. 144, lines 37-41).

Claim 4 is directed towards a third replication by repeating steps (e) through (g); Ladner teaches the third replicated series of steps (col. 144, lines 41-60).

As in claim 8, Ladner teaches adding an additional amount of target (*i.e.*, adding to an additional amount of a 50% slurry of beads - col. 144, lines 34-36).

As in claim 9, Ladner teaches use of the MB phage which is an M13 type phage (col. 118, lines 5-33) – Landner teaches that these phage typically produce between 100 and 1000 progeny (col. 55, lines 40-44), and therefore meet the limitations of the claim.

As in claim 13, Ladner teaches a diverse library of 10^5 phage with 97.4% of the approximately 97.4% possible DNA constructs – col. 143, lines 57-61.

As in claim 15, the phage of the KLMUT library each have a gene that allows for replication in the host cell (see col. 55, lines 28-44; col. 118, lines 5-35; and col. 144, lines 18-36).

As in claim 16, Ladner teaches that the phage may be selected from a phagemid (col. 76, lines 39-40), and that the use of a helper phage can be carried out (col. 60, lines 44-46).

As in claim 17, Ladner teaches the use of competing ligands to enhance identifying phage with desired properties (col. 98, lines 43-49)

As in independent claim 20, Ladner teaches (a) providing a bacteriophage library that comprises a plurality of bacteriophage members - (*i.e.*, KLMUT – a diverse library of over 1 x 10^5 phage – col. 143, lines 57-60;

(b) selecting a subset of the bacteriophage members – the step of binding the library of phage to the beads taught in Ladner; each phage displaying heterologous protease inhibitors which are considered diverse protein components, such as EpiNE1 through EpiNE8 (col. 142, line 14 through col. 143, line 56) having binding affinity for a target (*i.e.*, human neutrophil elastase) immobilized to a solid substrate (*i.e.*, agarose beads) – see col. 144, lines 15-36;

(c) infecting host cells with the members of the subset – Ladner teaches that the particle-bound phage are infected into XL1-Blue™ cells (col. 144, lines 28-30);

(d) amplifying members of the subset under at least one of the following conditions: (1) fewer than 5000 progeny phage are produced for each phage member selected in step (b) – Ladner teaches use of the MB phage which is an M13 type phage (col. 118, lines 5-33) – Ladner teaches that these phage typically produce between 100 and 1000 progeny (col. 55, lines 40-44);

(e) selecting a subset of amplified members, thereby identifying the desired members of the bacteriophage library – Ladner teaches the affinity maturation process wherein the selected phage reintroduced to cells and propagate, which are further selected and propagated (*i.e.*, amplified), and identification of clones having the greatest affinity (col. 144, lines 37-61).

As in claim 21, the amplification process and selection process of Ladner occur in the presence of the target as the bead-bound phage infect the host cells and progeny are produced, wherein the progengy phage bind the target (col. 144, lines 37-61). As in claims 22 and 23, Ladner teaches that the target (which can be the cells binding to the solid support as defined by Applicants' specification – see specification page 0038) binds to the solid support during amplification; contacting the library to the target and solid support, wherein the bacteriophage library members bind to the target through the solid support (*i.e.*, beads) – see col. 144, lines 18-36.

As in independent claim 24, Ladner teaches a method for selecting a nucleic acid that encodes a binding protein comprising:

(a) providing a library of phage that each have a heterologous protein component that is diverse among the phage of the plurality, physically attached to the phage, and accessible – Ladner teaches a method for screening a library of diverse phage (*i.e.*, KLMUT – a diverse library of over 1 x 10^5 phage – col. 143, lines 57-60), each phage displaying heterologous protease inhibitors which are considered diverse protein components, such as EpiNE1 through EpiNE8 (col. 142, line 14 through col. 143, line 56) having binding affinity for a target (*i.e.*, human neutrophil elastase) immobilized to a solid substrate (*i.e.*, agarose beads) – see col. 144, lines 15-36;

(b) contacting phage of the library to a target – as noted above, Ladner teaches that the library of phage are introduced to the bead-immobilized target HNE;

(c) performing one or more cycles of:

i) forming phage immobilized to a support, each of which comprises (1) a phage that binds to the target by its heterologous protein component and (2) the target immobilized to a support – Ladner teaches that certain optimized heterologous proteins, such as EpiNE7.8 (col. 144, lines 50-61), bind to the immobilized HNE target,

ii) separating phage that do not bind to the target from the phage immobilized to the support via binding to the target – Ladner teaches that the phage that do not bind to the target are washed away, leaving behind phage that bind the target,

iii) contacting phage from the phage immobilized to the support with host cells so that the host cells are infected by the phage from the immobilized to the support – Ladner teaches that these phage that are bound to the target on the beads are used to infect the XL1-Blue™ cells (col. 144, lines 28-47), and

iv) producing phage from the infected cells in the presence of target, the produced phage being replicates of phage that bind to the target – Ladner teaches that the recovered phage are replicates of the initial phage, but comprise a smaller library greater affinity/selectivity towards the HNE target, such as EpiNE7.8 as noted above; and

(d) recovering the nucleic acid encoding the heterologous protein of one or more produced phage - Ladner teaches recovering the nucleic acid (col. 144, lines 47-61).

As in claim 25, the conditions of separating the phage vary in stringency – Ladner teaches varying the pH (col. 144, lines 26-28).

As in claims 26 and 27, Ladner repeats the cycles of affinity maturation at least three times (col. 144, lines 15-61).

Although Ladner teaches performing his isolation of select phage bound to ligand-modified beads in reactions vessels, Ladner does not explicitly teach the use of the same target as carried out in step (a), such as a reusable target immobilized to a bead. Ladner also does not explicitly teach that the reactions are carried out in the same vessel, such as the steps of (a) through (g), or the steps of (d) to (e) in claims 5 and 6, respectively; and although Ladner discloses the addition of further target immobilized to the bead (*i.e.*, HNE), Ladner does not explicitly suggest that the reaction can be performed without additional target, as in claim 7.

Anderson teaches a method for using magnetic beads to isolate biological components of interest, wherein the component of interest binds to a target that is attached to the bead. Anderson teaches that the reactions used with the beads can be used to recover the target, and further utilize the target component of interest by manipulating the bead that it is attached to, and does not require further addition of more target-immobilized beads:

> "Once the protein is adsorbed to the beads, directly or via an affinity ligand, the composition is one of a denatured protein bound to the bead. The beads can be further manipulated by use of appropriate magnetic fields to perform processes such as digestion with protease, exposure to antibody mixtures in order to select those antibodies that specifically bind to the protein, and exposure to other proteins that may or may not be found to bind to the original protein."

Anderson, col. 11, lines 29-37; and the beads can be reacted and maintained in a single reaction vessel:

> "Instead of moving the beads to other vessels, one may collect the beads and aspirate, wash and change the solution in the same vessel for performing the next step."

Anderson, col. 29, lines 8-10.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Ladner and Anderson are directed towards techniques that utilize beads/reaction supports for the isolation of biological components that have affinity for given ligands. One of ordinary skill in the art would have recognized the

advantages of the single vessel approach used by Anderson in the phage targeting, isolation and growth as taught by Ladner, namely, the ease of use of having the selected biological component of interest contained to a single location that easily permits rapid addition and removal of reagents and reaction byproducts. Furthermore, one of ordinary skill in the art would have recognized the reusable nature of the beads as taught by Anderson, and recognized these advantages in the method of Ladner, such as reduced quantities of reagents. Therefore the invention as a whole was *prima facie* obvious at the time it was invented.

Claims 1-10, 12-17 and 20-28 are obvious over Ladner, Anderson and Janda:

Claims 1-10, 12-17 and 20-28, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ladner *et al.*, U.S. Patent No. 5,403,484 A, issued on April 4, 1995, in view of Anderson, U.S. Patent No. 6,649,419 B1, issued on November 18, 2003; and Janda, U.S. Patent No. 5,571,681 A, issued on November 5, 1996, is maintained in modified form. The rejection is modified in order to address Applicants amendment to the claim adding that the target is the same target as in step (a) of claim 1, namely, by combining with Anderson as explained above.

Applicants arguments traversing the rejection of Ladner and Janda (prior to amendment), and now presumably the instant rejection of Ladner, Anderson and Janda are for all practical purpose the same arguments that Applicants raised to the rejection of the claims over Ladner and Anderson.

Since the Examiner has addressed each of Applicants' arguments in the rejection above, and the rejection above is proper, the rejection of the claims over Ladner, Anderson and Janda is maintained for the reasons below.

The limitations of claims 1-9, 13, 15-17 and 20-27, and the corresponding teachings in Ladner and Anderson are presented above, and are hereby incorporated into the instant rejection.

Although Ladner provides certain general guidelines and conditions for reaction times involving the phage, Ladner does not explicitly teach reaction times of leas than 4 hours for step (e) or steps (d) and (f), as in claims 10 and 12, or the cycles being less than 8 hours as in claim 28; nor does Anderson. Ladner also does not explicitly teach a change in the temperature upon the producing step as in claim 14; nor does Anderson.

Janda generally teaches the use of covalent conjugates that are immobilized by attachment to a substrate through a solid phase and are easily separated from unconjugated elements of the combinatorial library by stringent washing. Janda generally teaches combinatorial libraries employing phagemid-display are particularly preferred since such phagemids include genetic material for identifying and amplifying conjugated catalysts. In describing the reactions for contact phage with the host cell, incubating the cell, and expressing the phage in the host cell, the processes can be carried out in less than four hours, such as the 15 minutes to infect the XL1-Blue™ cells, and the 2 hour culturing – note that the overnight cell selection with kanamycin is not required due to the beads being able to select the phage of interest an only captures progeny phage produced from the first round of binding to the bead that produced in the host cell (col. 25, lines 37-50). As in claim 14, Janda teaches going from room temperature during infection to 37 degrees C during incubation (col. 25, lines 37-50).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Ladner, Anderson and Janda are directed towards the use of methods for affinity selection of phage to a library of targets using bead-based strategies. Although Ladner does not explicitly recite the claimed time limitations or temperature change, such adjustments to those parameters are considered routine in the art, as exemplified by Janda, and are well within the purview of the ordinary artisan, especially considering that there is nothing in Applicants' disclosure that would present any objective indicia of non-obviousness (*e.g.*, there are no teachings of unexpected results based on the claimed limitations). Therefore, the invention as whole was *prima facie* obvious at the time it was invented.

Claims 1-9, 13, 15-18 and 20-27, are obvious over Ladner, Anderson and McCafferty:

Claims 1-9, 13, 15-18 and 20-27, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ladner *et al.*, U.S. Patent No. 5,403,484 A, issued on April 4, 1995, in view of Anderson, U.S. Patent No. 6,649,419 B1, issued on November 18, 2003; and McCafferty *et al.*, U.S. Patent No. 5,969,108 A, issued on October 19, 1999, is maintained in modified form. The rejection is modified in order to address Applicants amendment to the claim adding that the

target is the same target as in step (a) of claim 1, namely, by combining with Anderson as explained above.

Applicants arguments traversing the rejection of Ladner and McCafferty (prior to amendment), and now presumably the instant rejection of Ladner, Anderson and McCafferty are for all practical purpose the same arguments that Applicants raised to the rejection of the claims over Ladner and Anderson.

Since the Examiner has addressed each of Applicants' arguments in the rejection above, and the rejection above is proper, the rejection of the claims over Ladner, Anderson and McCafferty is maintained for the reasons below.

The limitations of claims 1-9, 13, 15-17 and 20-27, and the corresponding teachings in Ladner and Anderson are presented above, and are hereby incorporated into the instant rejection.

Although Ladner teaches the use of phage for producing a library of heterologous proteins with improved affinity, Ladner does not teach the use of mutator host strains as claimed in claim 18.

McCafferty teaches a member of a specific binding pair (sbp) is identified by expressing DNA encoding a genetically diverse population of such sbp members in recombinant host cells in which the sbp members are displayed in functional form at the surface of a secreted recombinant genetic display package (rgdp) containing DNA encoding the sbp member or a polypeptide component thereof, by virtue of the sbp member or a polypeptide component thereof being expressed as a fusion with a capsid component of the rgdp. The displayed sbps may be selected by affinity with a complementary sbp member, and the DNA recovered from selected rgdps for expression of the selected sbp members (see Abstract). McCafferty also uses subsequent rounds of selection and mutagenesis (col. 6, lines 1-5). Regarding mutagenesis, McCafferty teaches the value that mutator strains provide for combinatorial chemistry when using phage:

> "It will often be necessary to increase the diversity of a population of genes cloned for the display of their proteins on phage or to mutate an individual nucleotide sequence. Although in vitro or in vivo mutagenesis techniques could be used for either purpose, a particularly suitable method would be to use mutator strains. A mutator strain is a strain which contains a genetic defect which causes DNA replicated within it to be mutated with respect to its parent DNA. Hence if a population of genes as

> gene III fusions is introduced into these strains it will be further diversified and can then be transferred to a non-mutator strain, if desired, for display and selection."

McCafferty, col. 9, lines 50-61.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Ladner, Anderson and McCafferty are directed towards developing mutant heterologous polypeptides with phage display, wherein the selected phage have improved affinity/activity towards a given target. One of ordinary skill in the art would have been motivated to utilize a mutator strain as taught by McCafferty for the host cells of Ladner during the affinity maturation process because the mutator strains provide a convenient way to increase the diversity of genes used by the phage to display the library member. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Claims 1-17 and 20-28 are obvious over Ladner, Anderson, Janda and Steinbuchel:

Claims 1-17 and 20-28 rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner, Anderson and Janda as applied to claims 1-4, 8-10, 12-17, 20, 21 and 23-28 above, and further in view of Steinbuchel *et al.*, U.S. Patent No. 6,022,729, issued on February 8, 2000.

The limitations of claims 1-10, 12-17 and 20-28, and the corresponding teachings of Ladner, Anderson and Janda are detailed in the rejection above, and are hereby incorporated into the instant rejection.

Although each of Ladner and Janda each teach the use of the host cells XL1-Blue™ cells for preparing a phage library, and Janda teaches certain reaction times and temperatures, neither teaches that the host cells divide less than seven times as in claim 11.

Steinbuchel is directed to the use of certain host cells, such as XL1-Blue™ cells, for producing mutant polypeptide strains, wherein the host cells have been transfected with various constructs, such as pSKC07 and pSK2665 (see col. 14, lines 27-55). Over the course of cell growth, Steinbuchel shows the growth rate of the XL1-Blue™ cells under standard conditions (see Figure 5). As can be seen from Figure 5, the time for the host cell population to double, or

equivalently carry out one division on average, is between about 30 minutes (closed symbols) and less than four hours (open symbols)[1].

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Ladner and Janda are directed towards the use of methods for affinity selection of phage to a library of targets using bead-based strategies, and Steinbuchel is directed towards the use of the same host cells for producing mutant polypeptides. Although Ladner does not explicitly recited the claimed time limitations or temperature change (nor Anderson), such adjustments to those parameters are considered routine in the art, as exemplified by Janda, or the growth rate of XL1-Blue ™ cells within the time frame of Janda resulting in less than seven divisions, and are well within the purview of the ordinary artisan, especially considering that there is nothing in Applicants' disclosure that would present and objective indicia of non-obviousness (e.g., there are no teachings of unexpected results based on the claimed limitations). Therefore, the invention as whole was *prima facie* obvious at the time it was invented.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusions

No claim is allowable.

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[1] The graph is plotted as optical density which equivalent to an absorbance measurement produced from the XL1-Blue™ cells, where A = abc; (A, absorbance; a, molar absorptivity; b, path length, and c, concentration of host cells)

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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– therefore, a doubling in the OD is a result of a doubling of the concentration/number of the host cells, or one cell

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Patent Examiner, Art Unit 1639

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division.